REMARKS

Claims 91-133 were pending in the subject application. Of these, applicant by this Amendment has canceled claims 97-105 and 113-118 without prejudice, amended claims 91-93, 111 and 127, and added new claims 141-154. Accordingly, claims 91-96, 106-112, 119-133 and 141-154 are pending in the subject application.

Support for the amendment to claim 1 may be found, *inter alia*, on page 2, line 24 to page 3, line 27 of the subject application, where applicant's description shows that one skilled in the art commonly uses the term "small-molecule".

Support for new claims 141 and 142 may be found, *inter alia*, on page 12, lines 32-35 of the subject application.

Support for new claims 143-146 may be found, *inter alia*, in Figure 10, on page 20, line 8 to page 21, line 10, and page 30, line 35 to page 31, line 28 of the subject application.

Support for new claims 147-150 may be found, *inter alia*, in figure 6 of the subject application.

Support for new claims 151 and 152 may be found, *inter alia*, on page 4, line 29 to page 5, line 19 and on page 30, line 23-32 of the subject application.

Support for new claims 153 and 154 may be found, *inter alia*, on page 24, lines 1-21 of the subject application.

Election Requirement

The Examiner maintained and made final the September 5, 2002 restriction requirement.

In response, applicant notes that the Examiner acknowledged applicant's request for rejoinder and looks forward to rejoinder of claims 128-133 upon indication of allowable linking claims.

Objections to the Specification

In Section 6 of the December 31, 2002 Office Action, the Examiner objected to the specification on the basis that the status of parent application U.S. Serial No. 09/490,320 has not been indicated as "now abandoned".

In response, applicant has by this Amendment updated the status of U.S. Serial No. 09/490,320 on the first page of the substitute specification. Accordingly, this objection is moot.

In Section 7 of the December 31, 2002 Office Action, the Examiner objected to the Abstract, suggesting that the Abstract be amended to include dexamethasone and methotrexate as two integral "handles" in the hybrid assay system.

In response, applicant has submitted with this Amendment as **Exhibit 3** a substitute Abstract of the Invention.

In Section 8 of the December 31, 2002 Office Action, the Examiner objected to the citation of references throughout the specification for the following reasons:

A) beginning on page 62, the references are inconsistent in their citation with bold and italics used without clarity. Some reference contain titles while others do not.

B) if two or more publications are listed by the same auther in the same year (Belshaw, Galleni, Stemmer, and Stockwell), the designation "a,b,c" after the publication year is required to distinguish between the citations.

C) on page 62, the Bolin reference is incorrect; Filman is the first author and Hamlin is not an author.

D) on page 63, the Caldwell reference is incomplete without a title.

E) on page 63, the DeGrado reference notes "and following articles" which is inappropriate in a reference section.

F) on page 67, the Lin reference in preparation must have a completed reference at this time. Correction on the publication date in the specification is also required on page 40.

G) on page 68, the reference starting "*The chemistry of b-lactams*" is inappropriately cited.

H) throughout the specification, references are improperly cited by only the author; a publication year must be included with each reference throughout the specification for clarity.

In response, applicant has amended the specification consistent with the Examiner's suggestions, and submits herewith a substitute specification incorporating the amendments. Accordingly, the objection is moot.

Objections to the Claims

In Section 9 of the December 31, 2002 Office Action, the Examiner objected to claim 91 for a misspelling of "methotrexate".

In response, the spelling of "methotrexate" in claim 91 has been corrected by this Amendment.

In Section 10 of the December 31, 2002 Office Action, the Examiner objected to claim 127 for having a comma after "cerevisiae". In response, applicant has removed the comma.

In Section 11 of the December 31, 2002 Office Action, the Examiner objected to claims 106-110 for depending from rejected claims. In response, applicant appreciates the Examiner pointing out allowable subject matter. In addition, applicant has also amended the claims from which claims 106-110 depend so as the make all claims free of rejections as discussed below.

Rejection under 35 U.S.C. § 112, second paragraph

In Section 12 of the December 31, 2002 Office Action, the Examiner rejected claims 91-93, 97-105 and 111-127 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated that in claims 91-93 the term "analog" is used with respect to methotrexate or dexamethasone and that both are complex structures making the breadth of the term "analog" unclear. The Examiner also inquired whether a structural analog, a functional analog or both are meant.

In response, applicant has amended claims 91 and 111 to clarify that the analog of Mtx binds in a cell to dihydrofolate reductase (DHFR); and has amended claims 92 and 93 to no longer recite an analog in these two dependent claims. As amended, claims 91 and 111 are clear as to their metes and bounds because each provides a specific and definite functional definition for the recited analog.

Accordingly, claims 91 and 111 and all of the claims dependent thereon, comply with 35 U.S.C. § 112, second paragraph, and this rejection should be withdrawn.

In Section 13 of the December 31, 2002 Office Action, the Examiner rejected claims 92-105 and 111-127 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleged that the abbreviations "Dex", "Mtx", "LexA" and "B42" have not been defined in the claims and required correction.

In response, applicant has amended the claims to include the definition for the abbreviations "Dex" and "Mtx". However, LexA and B42 are not abbreviations. Rather LexA is the name of a specific DNA-binding protein, and B42 is the name of a specific activation domain.

Accordingly, claims 92-105 and 111-127 comply with 35 U.S.C. § 112, second paragraph, and this rejection should be withdrawn.

In Section 14 of the December 31, 2002 Office Action, the

Examiner rejected claims 119 and 121 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleged that the parentheses around "DNA-binding domain" and "transcription activation domain" are unclear in their meaning.

In response, applicant points out that the parentheses indicate that the words inside specify a single entity, which entity is bound to something else. If the parentheses were not used, in the case of "DNA-binding domain", the notation would be "DHFR-DNA-binding domain", making it unclear whether the DHFR is bound to a "DNA" which is bound to a "binding domain", or whether the DHFR is bound to a "DNA-binding domain". To avoid unnecessary confusion, applicant has chosen the notation with parentheses, i.e. "DHFR-(DNA-binding domain)". This terminology is well known to those familiar with the yeast two-hybrid system and yeast three-hybrid system. Any suggestions from the Examiner to achieve the required clarity without the use of parentheses would be welcome.

Accordingly, claims 119 and 121, as written, comply with 35 U.S.C. § 112, second paragraph, and this rejection should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph
Written Description

In Section 15 of the December 31, 2002 Office Action, the Examiner rejected claims 91-94, 97-105, 111-122 and 125-127 under 35 U.S.C. § 112, first paragraph, written description,

as allegedly containing subject matter which was allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner noted that the claims are drawn to compounds, complexes comprising said compounds, or cells comprising said complexes wherein the compounds are described by sub-compounds using functional language alone without any alleged particular, clear structural limitations, including the H1 moiety without a clear definition of a methotrexate analog as alleged above in the rejection under 35 U.S.C. §112, second paragraph and the H2 moiety.

The Examiner noted that the Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function

and structure, or a combination of these.

The Examiner noted that in the instant specification, dimerizing compounds are generally described as comprising two ends (H1 and H2) and a linker (Y) wherein the two ends each recognize different proteins and/or receptors, and specific examples of such compounds are also described using receptor-recognizing agents (i.e., ligands) like methotrexate, which recognizes dihydrofolate reductase (DHFR), and dexamethasone, which recognizes rat glucocorticoid receptor (rGR). The Examiner acknowledged that the art is replete with examples of receptor-recognizing agents or ligands; however, no generic structure can be described to encompass the entire genus. The Examiner noted that while the linker region is adequately described since its function is limited, any structure "capable of binding to a receptor" is an extremely broad genus that allegedly lacks adequate written description in the instant specification. On this basis, the Examiner alleged that one of skill in the art would be unable to predict the structures of other dimerizing compounds that meet the limitations of the claims on description in the instant specification and the knowledge in the art.

With respect to claims 97-105 and 113-118, the Examiner stated that the issue concerning written description is related to a specific function. The Examiner alleged that, for claims drawn to ligands having a particular affinity (IC50) for its receptor and/or protein, no particular structure is correlated with such an affinity, other than by way of example. Thus, the Examiner alleged, it would be impossible for one of skill in the art to predict the subset of ligands that will bind to

their receptors and/or proteins with an affinity of 1 nM, for example, as claimed in claim 105.

With respect to claims 111 and 125-127, the Examiner stated that the issue concerning written description is related to a specific function. The Examiner alleged that, for claims drawn to complexes comprising fusion proteins that contain "a binding domain capable of binding to methotrexate", no particular structure is correlated with such an affinity, other than by way of example. Thus, the Examiner alleged, it would be impossible for one of skill in the art to predict the subset of proteins that will bind to methotrexate.

In response, applicants have amended claims 91, 92, 93 and 111 to recite that H1 is methotrexate (Mtx) or an analog thereof that binds in a cell to dihydrofolate reductase (DHFR); and that H2 is a portion of the compound which is tested for binding to a receptor.

Initially, applicant notes that the Examiner has carefully reviewed this lengthy specification, as well as the prior art, and has understood that applicant is the first to use methotrexate as one of two members of a heterodimer molecule in a yeast three-hybrid system. In the comments regarding allowable subject matter in Section 19 of the Office Action, the Examiner has also noted the benefits of using methotrexate, specifically its high affinity to DHFR. This discovery by applicant allows for significant improvements in the yeast three-hybrid system, which, of course, is used to screen for a variety of interactions between the second member of the heterodimer, i.e. H2, and its receptor. Hence, by

definition of the yeast three-hybrid system, H2 must remain highly variable for one to practice the full scope of benefits stemming from applicant's invention.

To the extent this written description rejection and the following scope of enablement rejection apply to H2, applicant has amended the claims to overcome the rejections without unduly limiting the scope of applicant's invention. As noted, H2 must be permitted to remain highly variable in a yeast three-hybrid system.

Turning to H1 of the claimed compound, the clarification that the analog of methotrexate binds in a cell to DHFR makes the "analog" readily apparent to one skilled in the art. Specifically, the art is replete with disclosures of various methotrexate analogs that bind to DHFR. For example, after a cursory search of only the U.S. Patent database, the following ten (10) disclosures of methotrexate analogs were found: 5,958,928; 5,728,692; 5,698,556; 5,382,582; 5,354,753; 5,292,731; 4,725,687; 4,490,529; 4,374,987; and 4,057,584. In addition to these disclosures, many more disclosures of methotrexate analogs were readily available to those in this art as of the filing date of the subject application. One skilled in the art was then, and remains today, aware that methotrexate has been extensively studied and that a large disclosure of methotrexate analogs that bind to DHFR is readily available. The applicant was likewise aware as of the filing date of the subject application. As M.P.E.P. 2164.01 puts it, "a patent need not teach, and **preferably omits**, what is well known in the art." (emphasis added), citing *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir.

1991); and *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). M.P.E.P 2163(II)(a)(3) confirms that "what is conventional or **well known** to one of ordinary skill in the art need not be disclosed in detail" (emphasis added), again referring to *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. Therefore, with respect to H1, applicant respectfully submits that the claims, as amended, satisfy the requirements of 35 U.S.C. § 112, first paragraph, written description.

Turning to H2 of the claimed compound, applicant has clarified that H2 is a portion of the compound which is tested for binding to a receptor. This clarification avoids the functional requirement that the H2 bind to its target and precisely indicates to one familiar with yeast three-hybrid systems what H2 is. By avoiding the functional requirement that H2 bind its target, the amended claims avoid any necessity that the specification provide any description of receptor-recognizing ligands, i.e. making this rejection moot as to H2.

With respect to the rejection of claims 97-105 and 113-118, applicant has canceled claims 97-105 and 113-118 solely to advance prosecution of the subject application, but without conceding the correctness of the Examiner's position and without prejudice to applicant's right to pursue the subject matter of these claims. Accordingly, this rejection under 35 U.S.C. § 112, first paragraph, as to claims 97-105 and 113-118 is moot.

Turning to the rejection of claims 111 and 125-127 for reciting "a binding domain capable of binding to methotrexate", which the Examiner explained raises an issue concerning written description as related to a specific function, applicant points out once again that the specification adequately describes the binding domain. The Examiner correctly notes that the specification provides examples of "a binding domain capable of binding to methotrexate". Such examples must be taken with the extensive knowledge in the art of domains that bind to methotrexate. As applicant has explained in connection with H1 above, there is no requirement in patent law to list every possible example that achieves the desired function. The Examiner appears to be well aware that no *per se* prohibition of functional language exists in the patent law. Hence, applicant understands the issue raised by the Examiner to be one of breadth, as indicated by the Examiner's reliance on the case of *University of California v. Eli Lilly*, 119 F.3d 1559 (Fed. Cir. 1997) (the "UC" case).

Applicant's instant situation, however, has an important factual distinction over this UC case. UC claimed a genus covering human insulin cDNA, while the description only disclosed rat insulin cDNA. Importantly, the art in the UC case did not contain disclosure of any other insulin cDNA, i.e. the claim was wholly supported by UC's disclosure of rat insulin cDNA. Applicant's recited "binding domain", on the other hand, benefits from the extensive knowledge in the art about binding domains that bind to methotrexate. Applicant's invention utilizes the extensive knowledge in the art, whereas in the UC case the requisite knowledge was lacking in the art.

Accordingly, reliance on the UC case is not instructive.

Rather, other case bear more relevance to applicant's instant situation. For example, M.P.E.P. § 2173.05(g) cites to a case where the functional language "incapable of forming a dye with said oxidizing developing agent" was found "perfectly acceptable". *In re Barr*, 444 F2d 588 (CCPA 1971). In Barr, numerous compounds were known in the art which satisfied the functional requirement that they be "incapable of forming a dye with said oxidizing developing agent". The court in Barr also noted that Barr used a functional limitation to capture a broad class of known compounds, which Barr was using in his "combination" invention. This, of course in not unlike applicant's instant situation.

Therefore, applicant's recitation of a specific function in claims 111 and 125-127 is in full compliance with the written description standard.

Accordingly, applicant's claims, as amended, comply with 35 U.S.C. § 112, first paragraph, written description, and this rejection should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph
Enablement - claims 91-94, 97-105, 111-122 and 125-127

In Section 16 of the December 31, 2002 Office Action, the Examiner rejected claims 91-94, 97-105, 111-122 and 125-127 under 35 U.S.C. § 112, first paragraph, scope of enablement, alleging that the specification, while being enabling for compounds comprising structures known to recognize known receptors, does not reasonably provide enablement for

compounds comprising unknown structures thought to recognize unknown receptors. The Examiner alleged that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The Examiner alleged that the ability to produce the full scope of receptor-ligand pairs wherein the ligands can be used as a portion of the claimed dimerizing compounds would require undue experimentation.

The Examiner noted that the factors to be considered in determining whether experimentation is required are summarized in *In re Wands* F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). The Examiner referred to the court in Wands stating that "enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'." (Wands, 8 USPQ2d 1404) . . . "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The Examiner summarized the factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Examiner then noted that while all of these

factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The Examiner then alleged that, while the state of the art contains numerous examples of receptor-ligand pairs, many of which ligands would be easily used in the dimerizing compounds claimed, the specification provided no guidance or working examples for the production of all (or an enabling portion of the claimed genus) of new receptor-ligand pairs. The Examiner noted that the nature of the invention is such that screening procedures are available to identify such receptor-ligands pairs; however, the predictability of determining appropriate ligands and/or receptors is very low. On this basis, the Examiner asserted that applicant's claims are not enabled to the full extent of their scope.

In response, applicants have amended claims 91 and 111 to clarify that H2 is a portion of the compound which is tested for binding to a receptor. This clarification avoids the functional requirement that the H2 bind to its target and precisely indicates to one familiar with yeast three-hybrid systems what H2 is. By avoiding the functional requirement that H2 bind its target, amended claims 91 and 111 avoid the necessity that the specification describe "all" receptor-ligand pairs. All that the amended definition of H2 requires is that one skilled in the art be able to make and use the claimed compound. Clearly, one skilled in the art can *make* a compound according to applicant's formula H1-Y-H2 by known synthetic techniques, and then one can *use* the compound in the yeast three-hybrid system to test whether H2 can bind to a target.

With respect to the *Wands* factors, applicant respectfully submits that the factors must be analyzed in view of the extensive knowledge of scientist in academia and in industry who have used the yeast two-hybrid system, and the yeast three-hybrid system. Specifically, the quantity of experimentation necessary to change H2 to any desired molecule is low because no more than well known synthetic chemistry techniques are required. The amount or direction or guidance presented by applicant is sufficient to allow any synthetic chemist to make a large number of compounds with variant H2. Applicant has also disclosed in the specification a number of possible candidates for the H2 position, e.g. on page 29-30 of the original specification, all of which can be readily linked to H1. The nature of the invention, as noted above, is the recognition of methotrexate as a very useful anchor in a well known and studied yeast three-hybrid system, which recognition raises no issues of enablement not previously resolved in the art. The state of the prior art yeast three-hybrid system is well studied and widely used. The relative skill of those in the art is high. The predictability of the art is high once, as here, the functionality of H1 is established - the variability of H2 is precisely what the yeast three-hybrid art is concerned with. The breadth of applicant's claims is consistent with the applicant's invention. In summary, the *Wands* factors are consistent with an enabled invention.

Accordingly, applicant's claims, as amended, comply with 35 U.S.C. § 112, first paragraph, enablement, and this rejection should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph
Enablement - claims 97-105 and 113-118

In Section 17 of the December 31, 2002 Office Action, the Examiner rejected claims 97-105 and 113-118 under 35 U.S.C. § 112, first paragraph, scope of enablement, on the stated basis that while the specification is enabling for compounds and fusion proteins known to bind each other with particular affinities, does not reasonably provide enablement for compounds and fusion proteins which are not known to have the particular affinities recited in these claims.

In response, without conceding the correctness of the Examiner's position and without prejudice to applicant's right to pursue the subject matter of these claims, applicant has canceled claims 97-105 and 113-118 solely to advance prosecution of the subject application. Accordingly, this rejection under 35 U.S.C. § 112, first paragraph, is moot.

Rejection Under 35 U.S.C. § 102

In Section 18 of the December 31, 2002 Office Action, the Examiner rejected claims 91-94 and 97-100 under 35 U.S.C. § 102 as allegedly anticipated by Khawli et al, from applicant's IDS, ref. #4. The instant claims are drawn to compounds H1-Y-H2 where H1 is methotrexate and H2 is anything that binds a receptor or protein (based on the lack of clarity of the term dexamethosone analog as noted above in the rejection under 35 U.S.C. §112, second paragraph) with an affinity less than 100µ-M. The Examiner alleged that Khawli et al. teach methotrexate-conjugated antibodies (see column 16, line 5), and in its Example 20, methotrexate is conjugated to a monoclonal antibody that recognizes an antigen found in human pancreatic tumors. Based on the common scientific knowledge

of the high affinity of monoclonal antibodies and based on the effectiveness of the protocol taught by Khawli et al. (see column 17, lines 52-55), the Examiner asserted that an inherent affinity of the monoclonal antibody moiety is at least 100μ-M.

In response, applicant has amended claim 91 to recite that H2 is a "small-molecule". Claims 92-94 depend on and incorporate the limitations of claim 91, and claims 97-100 have been canceled without prejudice. A "small-molecule" clearly excludes a monoclonal antibody, such as that of Khawli et al., as understood in by one skilled in the art. Applicant provides a description of what one skilled in the art understands by "small-molecule" throughout the specification, in particular on page 2, line 24 to page 3, line 27. Accordingly, as amended claims 91-94 clearly distinguish over Khawli et al. and the rejection under 35 U.S.C. § 102 should be withdrawn.

No fee, other than the enclosed $55.00 fee for a one-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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